

## **REMARKS**

Applicants respectfully request entry of the above amendments and reconsideration of the following arguments pursuant to 37 C.F.R. § 1.111.

### **1. Status of the Claims**

Claims 1-35 stand pending. Claims 1-11, 13-14, 17-22, 24-25, and 28-35 stand withdrawn. Claims 12, 15-16, 23, and 26-27 stand rejected. Claims 12, 15-16, 23, and 26-27 stand objected to.

Applicants amend claims 1-15 and 16-35 to more precisely recite the claimed subject matter. For example, claims 3-5, 10-12, 18-20, 25-26, and 28-30 are amended to provide antecedent basis for the phrase “fusion protein.”

### **2. Petition**

For expediting prosecution in an effective fashion, Applicants file herewith a Petition under 37 C.F.R. § 1.144 to review the restriction requirement in view of the presently amended claims. Applicants respectfully request that any response be delayed until a decision on the Petition is rendered.

### **3. Support for the Amendments**

Support for the amendments can be found at least, for example, in the originally filed claims. Support for the amendment to claim 1 can be found at least, for example, from the originally filed claims 1 and 10-11, and on page 25, lines 21-27 of the Specification. Support for the amendment to claims 1-3, 8, 12, 15-16, 18, 23, 27-30, and 34-35, reciting “*E. coli* OmpT protease,” can be found at least, for example, on page 7, lines 34-37 of the Specification.

Applicants submit that no prohibited new matter is introduced by entry of the present amendments. Additionally, the claims have been amended without prejudice to, or disclaimer of, the canceled subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter canceled by way of amendment.

**4. Acknowledgement of Certified Priority Documents**

Applicants note with appreciation the indication that the certified priority documents have been received in the instant application.

**5. Acknowledgement of Information Disclosure Statements**

Applicants note with appreciation the acknowledgement of the Information Disclosure Statements (IDS) filed November 15, 2007; and March 28, 2006.

In the acknowledged copy of IDS filed November 15, 2007, the Office strikes out the Search Report dated December 13, 2004 ["Search Report"]. The Office further alleges that the Search Report has not been provided. Office Action, pages 3-4. The Office is respectfully reminded that the Search Report was submitted on March 28, 2006, when the national stage application was filed. Accordingly, the Office is respectfully requested to acknowledge the Search Report on the IDS filed November 15, 2007.

Applicants submit herewith an IDS containing (1) European Patent Application No. 1 076 097 A1, and (2) U.S. Patent No. 7,344,856.

**6. Claim of Priority**

The Office states that "[i]f Applicants wish the examiner to consider JP 2003-342183, filed September 30, 2003, an English translation should be filed." Office Action, page 3.

Applicants note that no English language copy of the priority document is required *unless* needed for the purpose of overcoming the effective date of a reference. *See* M.P.E.P. § 201.15. Accordingly, an English language translation is not required at this time, and the present application enjoys the benefit of priority to JP 2003-342183.

**7. Request for Status of Drawings**

Applicants respectfully request status as to the acceptance of the as-filed drawings with the Office's next communication.

**8. Species Election**

The Office acknowledges the election with traverse in Applicants' Response of April 3,

2009. Office Action, page 2. The Office, however, fails to respond to Applicants' argument, *inter alia*, that a special technical feature unites the claims. The Office, by referring to two other cleavage motifs as disclosed in Okuno et al., 2002, alleges that claim 1 is anticipated by the motifs. *Id.*, at 2-3. The Office then maintains that the restriction requirement is proper due to lack of a special feature to support unity of invention. *Id.*, at 3. Furthermore, the Office withdraws claims 1-11, 13-14, 17-22, 24-25, and 28-35 from further consideration, alleging that these claims are drawn to non-elected inventions. *Id.*

Applicants point out that the Office's assertion remains unsupported. A prior art reference cannot anticipate a claim unless the prior art discloses, explicitly or inherently, each and every element of the claim. *In re Spada*, 911 F.2d 705, 708, 15 U.S.P.Q.2d 1655, 1657 (Fed. Cir. 1990). In the present application, "Okuno et al., 2002" allegedly discloses cleavage motifs that anticipate the motifs recited in claim 1. The Office apparently refers to **Okuno** et al., 36 BIOTECHNOL. APPL. BIOCHEM. 77 (2002) ["Okuno I"], instead of **Okuno** et al., 66 BIOSCI. BIOTECHNOL. BIOCHEM. 127 (2002) ["Okuno II"]. Nevertheless, neither "Okuno I" nor "Okuno II" anticipates the cleavage motifs recited in amended claim 1.

Claim 1 as amended recites, *inter alia*, a cleavage motif with the following features:

- 1) it has "a single basic amino acid or two or three consecutive basic amino acids situated at any site in the amino acid sequence from the P10 position to the P3 position or from the P3' position to the P5' position," *and*
- 2) "if there is only a single basic amino acid situated in the amino acid sequence from the P10 position to the P3 position, the single basic amino acid is situated at a position other than the P6 or the P4 position."

The alleged anticipatory cleavage site in the prior Office Action is "RLELYK↓RHHG" in Table 3 on page 83 of Okuno I. This peptide motif does not anticipate the recited motifs in claim 1 and thereby destroy unity of invention, because:

- 1) it contains a single basic amino acid (**R**) situated in the amino acid sequence from the P10 position to the P3 position or from the P3' position to the P5' position; and
- 2) the basic amino acid (**R**) of the "RLELYK↓RHHG" motif is situated at the P6 position—*failing to comply with the second feature recited*

*in amended claim 1*, which recites, *inter alia*, that “the single basic amino acid is situated at a position **other than** the **P6** or the **P4** position.” (see illustration below)

<b>Cleavage Motif</b>	<b>R</b>	L	E	L	Y	K	↓	R	H	H	G
<b>Notation of Positions</b>	P6	P5	P4	P3	P2	P1		P1'	P2'	P3'	P4'

As the “**R**LELYK↓RHHG” motif fails to anticipate motifs recited in the amended claim 1, it cannot destroy unity of invention.

Similarly, the cleavage motif of Okuno II, “EL**R**LYK↓RHHG,” also fails to anticipate motifs recited in amended claim 1. The “EL**R**LYK↓RHHG” motif therefore cannot destroy unity. Although this motif contains a single basic amino acid (**R**) situated in the amino acid sequence from the P10 position to the P3 position or from the P3' position to the P5' position, the basic amino acid (**R**) of the “EL**R**LYK↓RHHG” motif is situated at the P4 position—*failing to comply with the second feature recited in amended claim 1* (see illustration below). The amended claim 1 recites, *inter alia*, “the single basic amino acid is situated at a position **other than** the P6 or the **P4** position.”

<b>Cleavage Motif</b>	E	L	<b>R</b>	L	Y	K	↓	R	H	H	G
<b>Notation of Positions</b>	P6	P5	P4	P3	P2	P1		P1'	P2'	P3'	P4'

Accordingly, the “EL**R**LYK↓RHHG” cannot destroy unity of invention, because it fails to anticipate the motifs recited in amended claim 1.

The Office alleges that the peptide motif “ELELYK↓RHHG” on Table 3 on page 83 of Okuno I anticipates the recited motifs. However, this motif lacks a single basic amino acid (R or K), and lacks two or three consecutive basic amino acids situated in the amino acid sequence from the P10 position to the P3 position or from the P3' position to the P5' position—*failing to comply with the first feature recited in amended claim 1* (see illustration below). The amended claim 1 recites, *inter alia*, a motif having “a single basic amino acid or two or three consecutive basic amino acids situated at any site in the amino acid sequence from the P10 position to the P3 position or from the P3' position to the P5' position.”

<b>Cleavage Motif</b>	E	L	E	L	Y	K	↓	R	H	H	G
<b>Notation of Positions</b>	P6	P5	P4	P3	P2	P1		P1'	P2'	P3'	P4'

Accordingly, the “ELELYK↓RHHG” motif cannot anticipate the motifs recited in the amended claim 1, and therefore cannot destroy unity of invention.

The Office further alleges that peptide motif “GYDAELALYR↓RHHG” in Fig. 1A on page 79 of Okuno I anticipates the recited motif. However, this motif lacks a single basic amino acid (R or K), and lacks two or three consecutive basic amino acids situated in the amino acid sequence from the P10 position to the P3 position or from the P3’ position to the P5’ position—*failing to comply with the first feature recited in amended claim 1* (see illustration below). The amended claim 1 recites, *inter alia*, a motif having “a single basic amino acid or two or three consecutive basic amino acids situated at any site in the amino acid sequence from the P10 position to the P3 position or from the P3’ position to the P5’ position.”

Cleavage Motif	G	Y	D	A	E	L	A	L	Y	R	↓	R	H	H	G
Notation of Positions	P10	P9	P8	P7	P6	P5	P4	P3	P2	P1		P1’	P2’	P3’	P4’

Accordingly, the “GYDAELALYR↓RHHG” motif cannot anticipate the motifs recited in the amended claim 1, and cannot destroy unity of invention. In sum, none of the cited peptide motifs anticipates the motifs recited in amended claim 1. Therefore, unity of invention is maintained for the amended claims.

Applicants again request that the Office either withdraw the objection to unity of invention in view of the above analysis or issue a rejection as to the alleged anticipation under 35 U.S.C. § 102, so that Applicants can fully respond. Applicants reserve the right to file a Petition under 37 C.F.R. § 1.144 on the Office’s position regarding species election in this matter.

## 9. Objection to the Claims

The Office states that “claims 12, 15-16, 23, and 26-27 are objected to for reciting non-elected subject matter.”

Applicants traverse the objection. On page 3 of the Office Action, the Office States that “claims 1-11, 13, 14, 17-22, 24, 25, and 28-35 are withdrawn from further consideration...as being drawn to nonelected inventions.” The claims that stand elected are pending. *The elected subject matter is a provisional election of species for search purposes only.* It would be premature to amend the claims to omit matter that merely is not currently being searched.

Additionally, the Office has not provided a procedural, regulatory, or statutory basis for the objection. Because the object is unauthorized, it should be withdrawn.

Applicants note that the restriction has been traversed. Applicants have maintained the right to petition the restriction. Applicants submit this is a *bona fide* attempt to respond to the objection. Applicants request clarification with the Office's next response or respectfully request withdrawal of the objection given the other arguments presented herein.

#### **10. Rejection of the Claims under 35 U.S.C. § 101**

The Office rejects claims 12, 15-16, 23, and 26-27 under 35 U.S.C. § 101 as allegedly failing to set forth any steps involved in the process and resulting in an improper definition of a process. Office Action, page 4.

Upon entry of the present claim amendments, each of claims 12, 15-16, 23, and 26-27 recites a process having at least one active step. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims in view of the amendments.

#### **11. Rejection of the Claims under 35 U.S.C. § 112, Second Paragraph**

##### **11.1. Indefiniteness Rejection I**

The Office rejects claims 12, 15-16, 23, and 26-27 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Office alleges that the claims do not set forth any step involved in the method / process. Office Action, pages 4-5.

Upon entry of the present claim amendments, each of claims 12, 15-16, 23, and 26-27 recites a process comprising at least one active step. Accordingly, the rejection should be withdrawn, and the claims allowed.

##### **11.2. Indefiniteness Rejection II**

The Office further rejects claims 12, 15-16, 23, and 26-27 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, because of the term "OmpT protease." The Office alleges that a skilled artisan would not know the metes and bounds of the recited invention. Office Action, page 5.

Applicants traverse the rejection to the extent it applies to the amended claims. “[T]he definiteness of the language employed must be analyzed—not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.” *See e.g., In re Moore*, 439 F.2d 1232, 1235, 169 U.S.P.Q. 236, 238 (C.C.P.A. 1971). The amended claims recite “*E. coli* OmpT protease,” the description of which can be found in the paragraph bridging pages 7-8 of the Specification. A skilled artisan would know the metes and bounds of the recited invention in light of the description in the Specification. Accordingly, the indefiniteness rejection should be withdrawn, and claims allowed in view of the amendments and the above arguments.

## **12. Rejection of the Claims under 35 U.S.C. § 112, First Paragraph**

### **12.1. Enablement Rejection**

The Office rejects claims 12, 15-16, 23, and 26-27 under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide enablement. The Office alleges that the present claims encompass an extremely large number of methods. Office Action, page 6. The Specification allegedly does not support the broad scope of the claims. The Office asserts that the Specification fails to establish:

- 1) the structural and functional metes and bounds of any OmpT protein;
- 2) all proteins that can be cleaved by the encompassed OmpT variants having a substitution at 97;
- 3) any protein comprising SEQ ID NO: 12 that can be cleaved using an OmpT variant having a substitution at residue 97;
- 4) regions of the OmpT protein structure that may, or may not, be modified without affecting the desired activity;
- 5) the general tolerance of the desired activity to modification of OmpT and extent of such tolerance;
- 6) a rational and predictable scheme for identifying, without undue experimentation, which motifs can be cleaved by all encompassed OmpT variants having a substitution at residue 97; and
- 7) the specification provides insufficient guidance as to which of the essentially infinite possible choices of combinations of OmpT variants and motifs is likely to be successful.

*Id.*, at 6-7. The Office asserts that results of amino acid modification are unpredictable. *Id.*, at 6.

Furthermore, the Office alleges that there is insufficient guidance for those skilled in the art to practice the claimed invention. *Id.*, at 7.

Applicants traverse rejection to the extent that it applies to the amended claims. The enablement requirement is satisfied when a skilled artisan, after reading the specification, could practice the claimed invention ***without undue experimentation***. See *In re Wands*, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Federal Circuit suggests following factors to be considered to determine whether the experimentation is undue: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See *Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Furthermore, the specification need not necessarily describe how to make and use ***every possible*** variant of the claimed invention, “for the artisan’s knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.” See *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 U.S.P.Q.2d 1280, 1287 (Fed. Cir. 2003).

***The nature of the invention and the breadth of the claims***

The present claims recite a polypeptide cleavage process or method comprising using a protease to cleave a polypeptide at a desired site. The protease can be an *E. coli* OmpT protease or a variant thereof having a substitution at the 97<sup>th</sup> amino acid position. The claims are not as broad as alleged by the Office to encompass infinite methods of cleavage, because both the enzymes and their substrates are specifically defined in the Specification. See pages 7-9 of the Specification.

***The state of the prior art; the relative skill of those in the art; and the predictability or unpredictability of the art***

At the time the present application was filed, there had been sufficient knowledge in the field regarding the structure-function relationship in *E. coli* OmpT protease. See Kramer et al. 505 FEBS LETT. 426 (2001) (listed in the IDS submitted March 28, 2006). The crystal structure of *E. coli* OmpT protease has been solved, and the structure, particularly the interaction between the enzymatic active site with the substrate, has provided rational design of *E. coli* OmpT

variants. *Id.* A skilled artisan would have been able to predict, based upon available knowledge regarding *E. coli* OmpT and protein structure-function relationship in general, whether a specific substitution would affect the function of the resulting variant.

Furthermore, the *E. coli* OmpT protease and other OmpT-like proteases from *Salmonella*, *Yersinia*, and *Shigella* are known to be members of the omptin family. Members of the omptin family share a high level of amino acid sequence identity. *See e.g.*, lines 26-33 on page 1 of the Specification. For example, *E. coli* OmpT protease contains 36 acidic residues, of which six aspartates (positions 43, 83, 85, 97, 208, and 210) and five glutamates (positions 27, 111, 136, 193, and 250) are ***fully conserved within the omptin family***. *See* page 426 and Fig. 1 of Kramer. Thus, knowledge obtained from an OmpT-like protease would be applicable to *E. coli* OmpT protease, *e.g.*, substitutions in the conserved regions are more likely to affect the enzyme's recognition and cleavage of a specific site in a polypeptide.

Accordingly, the skilled person would have had enough information at the time to make and use the claims.

***The presence or absence of working examples; the amount of direction or guidance presented; and the quantity of experimentation necessary***

The present Specification provides working examples in Examples 13-18 in which the *E. coli* OmpT variants with a substitution at the 97<sup>th</sup> amino acid position are used to cleave polypeptides with various cleavage motifs. *See* pages 44-67 of the Specification. Additionally, the present Specification provides, *inter alia*, detailed methods for (1) preparing the *E. coli* OmpT variants (*see e.g.*, Example 11), (2) preparing the substrate polypeptides or fusion proteins (*see e.g.*, Examples 1, 3, 5, 7, and 9), and (3) detecting and quantifying the cleavage activity or efficiency (*see e.g.*, line 26 on page 29 to line 11 on page 31; Examples 2, 4, 6, 8, and 10).

The experimentation would have been considered as ***routine*** to (1) prepare the *E. coli* OmpT variants, (2) characterize the cleavage specificity of the *E. coli* OmpT variants, (3) prepare various substrate polypeptides or fusion proteins, and (4) characterize the cleavage pattern of the substrate polypeptides or fusion proteins by *E. coli* OmpT variants. Accordingly, a skilled person, based upon the working examples and guidance provided by the present Specification, would have had sufficient guidance in order to perform the routine steps to make and use the process.

Furthermore, a skilled artisan, at the time the present application was filed, would have been able to employ the knowledge of the prior art and routine experimentation to “fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments.” *AK Steel*, 344 F.3d at 1244, 68 U.S.P.Q.2d at 1287.

Accordingly, there is no undue experimentation to practice the presently claimed methods. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

### **12.2. Written Description Rejection**

The Office rejects claims 12, 15-16, 23, and 26-27 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to demonstrate possession. The Office alleges that the Specification teaches (1) only a few representative species of the methods recited by claims 12, 15-16, 23, and 27, and (2) no methods recited by claim 26. Office Action, page 8.

Applicants traverse the rejection to the extent it applies to the amended claims. The Office misstates the standard for compliance with the written description requirement. The Office must follow the legal precedent of its reviewing courts. *See, e.g., In re Lee*, 277 F.3d 1338, 1344, 61 U.S.P.Q.2d 1430, 1434 (Fed. Cir. 2002) (citing cases and relying on *National Labor Relations Bd. v. Ashkenazy Property Mgt. Corp.*, 817 F.2d 74, 75 (9th Cir. 1987) (an agency is “not free to refuse to follow circuit precedent.”)). In the present case, the Federal Circuit explicitly holds that ***working examples*** covering the full scope of the claims are not required for an adequate written description:

A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.

*Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006). The Office’s requirement for specific examples for each and every variant encompassed by the claim ***explicitly contradicts*** this holding. For this reason alone, the rejection is improper and should be withdrawn.

Whether generic claims to biological subject matter comply with the written description requirement is determined by an analysis of the *Capon* factors: (1) the existing knowledge in the particular field, (2) the extent and content of the prior art, (3) the maturity of the science or technology, (4) the predictability of the subject matter at issue, and (5) other considerations appropriate to the subject matter. *See Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005); *Carnegie Mellon Univ. v. Hoffman-LaRoche Inc.*, 541 F.3d 1115, 88 U.S.P.Q.2d 1233 (Fed. Cir. 2008). Also relevant in this context is whether the disclosed species are representative of the claimed genus, such that the skilled artisan would recognize that Applicants possessed the “necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.” *See Carnegie*, 88 U.S.P.Q.2d at 1239.

In the present case, the Specification describes that (1) *E. coli* OmpT protease and other OmpT-like proteases from *Salmonella*, *Yersinia*, and *Shigella* are known to be members of the omptin family, which has been well characterized; (2) these proteases share significant amino acid sequence identity; (3) the crystal structure of *E. coli* OmpT has been published, providing a well-characterized relationship between structure and function; (4) the interaction between *E. coli* OmpT’s active site with its corresponding substrates has been studied in detail; and (5) there is standard knowledge in the field regarding the generation of variant proteases and various substrate peptides. *See e.g.*, lines 26-33 on page 1 and the paragraph bridging pages 27-28 of the Specification; *see also* Kramer *supra*; *see also* Vandeputte-Rutten et al., 20 EMBO J. 5033 (2001), and Stathopoulos, 12 MEMBR. CELL BIOL. 1 (1998). The Specification thus provides sufficient description for the presently recited methods. *See Capon* factors (1)-(4).

For all the forgoing reasons, amended claims 12, 16, 23, and 26-27 comply with the written description requirement. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

### CONCLUSION

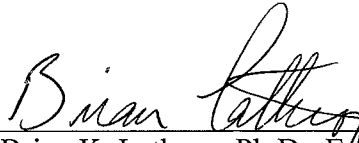
Should the Examiner have any questions or comments regarding Applicants' amendments or response, please contact Applicants' undersigned representative at (202) 842-8862. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number.

Respectfully Submitted,

Date: September 14, 2009

By: \_\_\_\_\_

  
Brian K. Lathrop, Ph.D., Esq.  
Registration No. 43,740

DRINKER BIDDLE & REATH LLP  
Customer No. **55694**  
1500 K Street, N.W., Suite 1100  
Washington, D.C. 20005-1209  
Tel. No.: (202) 842-8800  
Fax No.: (202) 842-8465